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REVIEW

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# HIV/SARS-CoV-2 coinfection: A global perspective

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## Abstract

Since its first appearance in Wuhan, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread throughout the world and has become a global pandemic. Several medical comorbidities have been identified as risk factors for coronavirus disease 2019 (COVID-19). However, it remains unclear whether people living with human immunodefeciency virus (PLWH) are at an increased risk of COVID-19 and severe disease manifestation, with controversial suggestion that HIV-infected individuals could be protected from severe COVID-19 by means of antiretroviral therapy or HIV-related immunosuppression. Several cases of coinfection with HIV and SARS-CoV-2 have been reported from different parts of the globe. This review seeks to provide a holistic overview of SARS-CoV-2 infection in PLWH.

**KEYWORDS**

antiretroviral therapy/coinfection, COVID-19, HIV, immunodeficiency

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a potentially fatal respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly identified coronavirus, which was first recognized in December 2019 in Wuhan, Hubei Province, China and has since rapidly spread to over 200 countries/territories/areas and have been declared a global pandemic by the World Health Organization (WHO).[1] As at the time of writing (3 June 2020), the total confirmed cases were 6 383 805 with 2 732 976 recoveries and a staggering 380 384 deaths have been officially reported globally.[2] The clinical spectrum of COVID-19 is broad, and while most people with COVID-19 develop only mild or uncomplicated illness, especially in the early phase of illness, 14% to 26% of infected persons develop severe disease that requires hospitalization and oxygen support, with some even requiring admission to an intensive care unit.[3,4] Organ dysfunction, particularly progressive respiratory failure, heart and kidney injuries, is associated with the highest rates of mortality.[5,6] Clinical evidence has shown that disease severity and mortality are associated with older age and underlying comorbidities, such as diabetes, hypertension, and cardiovascular disease (CVD).[4,6,7] In line with this, one of the puzzling questions in the wake of this pandemic is "Does HIV infection increases the risk of getting and disease severity of COVID-19?." This is important, especially in Africa, as the region accounts for more than 70% of the global burden of human immunodefeciency virus (HIV) infection.[8] Generally, people living with HIV (PLWH) are perceived to be at high risk of contracting SARS-CoV-2, even though currently no specific information about the risk of COVID-19 in people with HIV is available. At the end of 2018, it was estimated that 37.9 million people globally were living with HIV with 20.6 million (54%) in the eastern and southern Africa region, 5.9 million in Asia and the Pacific region, 5.0 million in western and central Africa, and 2.2 million in western and central Europe and north America region.[9] In an attempt to halt the spread of COVID-19, governments across the globe are shutting cities down, restricting movements and encouraging residents to stay indoors. Beyond the unprecedented disruption of lives, the COVID-19 pandemic has severely interrupted HIV care delivery among several other health care services globally as attention, resources and personnel have been diverted to the fight against COVID-19.[10-12] It is estimated that about 19% of HIV-infected patients were unable to get antiretroviral medications or therapy (ART) refills due to the

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pandemic. In addition, there have been reports that several HIV/AIDS prevention and control centers globally have been converted to COVID-19 treatment centers, which denies HIV patients of their ART.[13-15] This has left a greater proportion of the HIV community in a venerable state, considering that they require regular medication to maintain good health. Despite the potentially poor prognosis for most patients within this category when infected with SARS-CoV-2, data on HIV/SARS-CoV-2 co-infection is still scarce. Herein we summarize the global instances of SARS-CoV-2/HIV coinfections.

### 1.1 | General impact of COVID-19 on patients with HIV

The COVID-19 pandemic, as well as measures taken by governments across the world, to minimize its spread has triggered unintended consequences in terms of HIV testing and care.[16] The Euroguidelines in Central and Eastern Europe Network Group recently found that 60% of HIV physicians simultaneously are involved in work related to patients with COVID-19. In the worst scenarios, they abandon their original duties entirely and engage fully in COVID-19 cases.[17] Moreover, to compensate for the increasing numbers of recorded cases (patients), HIV treatment facilities have been designated as COVID 19 care centers. According to Kowalska and coworkers, about 70% of HIV treatment facilities in central and Eastern Europe were not functioning due to COVID-19.[17] This together with the fear of contracting COVID-19 have kept many patient with HIV from accessing their usual ART. The Lancet HIV recently reported that HIV patients in Egypt are petrified to go for their ART refills because the only HIV treatment Center, have been converted to COVID-19 quarantine and treatment facility.[18] In the Hubei province of China, about 64.15% of HIV patients could not have access to their ART due to the measures imitated to curb the spread of the virus.[19] As Gokengin et al reported, antiretrovirals are purchased and distributed via designated clinics [20] thus, patients living outside the perimeter could not have access to their ART. The situation is further aggravated by shortage of medication as medical consignments are stuck in procurement systems in other countries with no further supplies able to come in.[21] The pandemic has as well compromised the psychological and emotional wellbeing of PLWH. Shiau et al[22] reported that many HIV patient being managed via telephone have indicated that they are extremely stressed, anxious, and unable to sleep. A recent survey in China,[19] revealed that 28.93% of the respondents hoped they had some social and psychological support. Therefore, these psychosocial issues have to be addressed to avoid exacerbating adverse medical consequence among PLWH.[22]

## 2 | METHODS

SCOPUS, Web of Science, PubMed and Google Scholar were searched for relevant peer-reviewed publications from December 2019 to 3 June 2020, using the following combination of terms: ("HIV" AND "COVID-19"), ("Immunodeficiency" AND "COVID-19") and ("HIV" AND "Coronavirus"). The search was limited to only publications in English. Publications with information on HIV/SARS-CoV-2 co-infection were manually sorted out and included in this study. Websites of relevant organizations including WHO, CDC, and USAIDS were also reviewed for additional information. Data on co-infection cases were extracted and entered into Microsoft Excel. Statistical analyses were carried out using IBM SPSS Statistics version 25.

## 3 | RESULTS AND DISCUSSION

The first case of HIV/SARS-CoV-2 coinfection was reported in Wuhan, China, the terminus a quo of the pandemic. Subsequent cases of coinfection have been reported in UK, USA, Spain, Italy, Germany and other countries (Table 1). Interestingly, only two cases of coinfection have been reported in the whole of the Africa continent, notwithstanding the fact that South Africa which is at present the epicenter of the COVID-19 pandemic in Africa[1] and home to over close to 8 million PLWH, the largest HIV epidemic in the world.[23] The situation of Africa is probably not because less PLWH have actually contracted COVID-19, but more likely due to unpublished data, taking into account the uncoordinated and poor data collection and management in hospitals and health centers, lack of enthusiasm and ability of most health professionals to conduct research and prepare manuscripts for publication as well as poor collaboration between researchers and health professionals. The region currently accounts for just a little of 1% of global health publications [24] with a significant part being championed by researchers from high income countries.[25] Nonetheless, 378 HIV/SARS-CoV-2 coinfection cases have so far been reported globally with a majority originating from UK (101 cases) and USA (122 cases). The high number of coinfection cases from these countries however does not particularly suggest any increased risk of COVID-19 among PLWH in them. It is worth noting that studies characterizing a larger population of patients with COVID-19 originated from these countries, and hence the high reported cases of coinfection. Similar to that observed in the general population, majority (72.3% of 334) of the COVID-19 cases in PLWH were males. While WHO earlier reported 51% of cases in China are males, studies from UK [26] and USA [27] indicated males represent up 60% of the COVID-19 cases. Also, among a total of 142 coinfection cases where information on age is available, 59.9% were in the range of 40 to 59 years (Figure 1) with 23.2% being under 40 years. Taking into consideration studies from Italy,[28] Spain,[29] Turkey [30] and UK [31] that characterizes COVID-19 in HIV cohorts (n = 12 296), the prevalence of HIV/SARS-CoV-2 coinfection is 0.98%. On the other hand, considering reports from China,[32-34] Japan,[35] Spain,[36] UK,[26] and USA,[27,37] PLWH account for only 0.64% of the general COVID-19 population (n = 26, 049; see supplementary data) as compared with 16.9% to 56.6% for CVD (including hypertension), 8.2% to 33.8% for diabetes and 1.5% to 17.7% for respiratory diseases.[26,27,38] This correlate to several studies among large populations which observed

**TABLE 1** Clinical characteristics of HIV/SARS-CoV-2 coinfected patients

| Country | HIV/COVID-19 coinfection | At least one comorbidity (n = 237) | ART before COVID-19 (n = 244) | Viral load < 50 (n = 216) | CD4 count > 200 (n = 188) | Reference |
|---|---|---|---|---|---|---|
| Austria | 1 | 1 | 1 | 1 | 1 | 47 |
| China | 9 | 1 | 4 | 0 | 2 | 33,34,45,48-52 |
| Cyprus | 1 | NA | 1 | 1 | 1 | 53 |
| Germany | 33 | 20 | 33 | 30 | 32 | 54 |
| Italy | 47 | 30 | 36 | 44 | 0 | 28 |
| Japan | 1 | NA | NA | 0 | 0 | 55 |
| Singapore | 1 | 0 | 1 | 1 | 1 | 56 |
| S. Africa | 1 | 1 | 1 | 1 | 0 | 57 |
| Spain | 56 | 34 | 55 | 54 | 49 | 29,36 |
| Turkey | 4 | 1 | 3 | 0 | 3 | 30 |
| Uganda | 1 | 0 | 1 | 0 | 1 | 8 |
| UK | 101 | 6 | 18 | 17 | 14 | 26,31 |
| USA | 122 | 57 | 74 | 54 | 60 | 27,37,40,41,58-62 |
| Overall | 378 | 151 | 228 | 203 | 164 | |

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodefeciency virus; NA, not available; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

that PLWH made up approximately less than 1% of COVID-19 cases.[26,27] The low proportion of PLWH among patients with COVID-19 should, however, be interpreted with caution as it could be as a result unyielding commitment to safety precautions (including wearing of nose masks, hand hygiene, social distancing, etc.) by individuals with HIV to limit their exposure to the SARS-CoV-2, bearing in mind their compromised immune system and the fact that even before COVID-19 they were at risk of a broad range of infections, including respiratory tract infections,[23] rather than protection afforded by HIV or ART. It could also be that less of the HIV population is being screened for COVID-19, looking at the fact some are not even enthused to visit treatment centers and clinics for their ART refills.[18] In general, 214 of a total 334 coinfection cases were uncomplicated (ie, mild and moderate) cases while the remaining 35.9% were classified as either severe or critical (complicated), requiring oxygen therapy and/or admission to intensive care unit (Figure 2). Among subjects with known outcomes (closed cases; n = 300) 82.3% had recovered while the remaining (53 patients) died, thus giving an overall case-fatality rate of 14% among PLWH, which is more than 2 times higher than the current rate among the global population.[1] However, just like the country-specific case-fatality ratio of COVID-19 in the general population, the case-fatality rate among PLWH differ from one country to another, ranging from as high as 27.7% in UK to 0% in China (Figure 3). Similar to UK, the results of the analysis indicated USA also has a high case-fatality ratio (13.9%) among its HIV population which is 2.4 time higher than that of the general population (5.8%).[39] Among the top five countries in terms of number of coinfection cases reported, the case-fatality ratio among PLWH in Spain (3.6%) and Italy (4.3%) are lower than that recorded for the general population, 11.3% and 14.4% respectively.[39] Compared with that of the general population of the country, the case-fatality rate among the HIV population in UK and Germany are almost two times higher. Differences in mortality numbers of COVID-19 among countries have been attributed to several factors including differences in number of people tested, demographic characteristics,

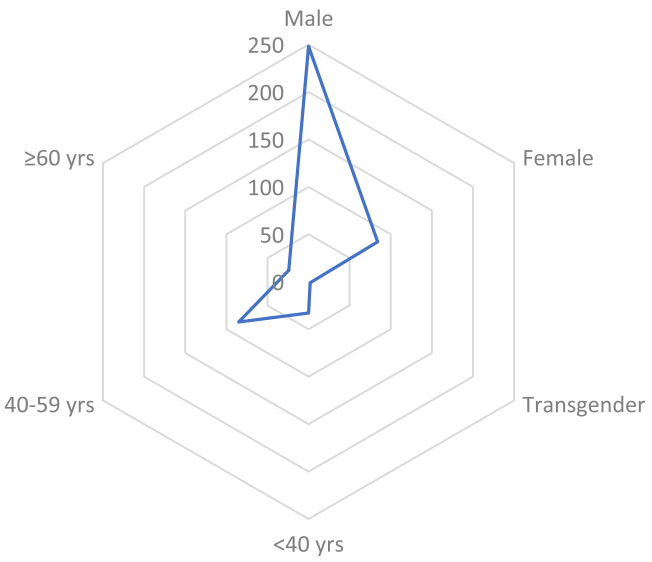


**FIGURE 1** Demographic characteristics of HIV/SARS-CoV-2 coinfected patients

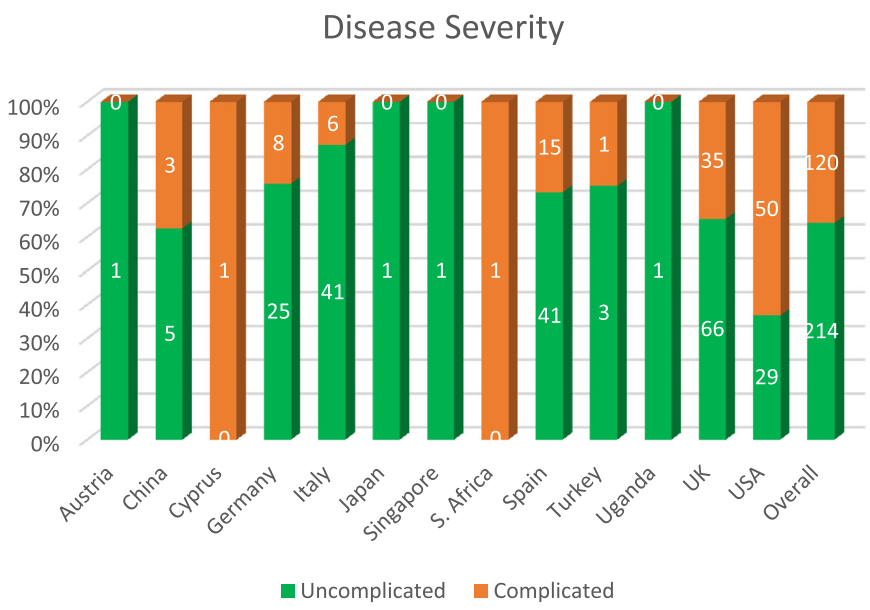


**FIGURE 2** Disease Severity associated with HIV/SARS-CoV-2 coinfected patients

characteristics of the healthcare system, among others.[39] Nonetheless, it should be noted that majority of the cases included in this study (particularly from UK and USA) were hospitalized patients and as such the high case-fatality rates recorded might not be particularly peculiar to HIV/SARS-CoV-2 coinfection since as much as 26% (in UK) [26] and 21% (in USA) [27] of hospitalized patients with COVID-19 were reported dead. Earlier reports on HIV/SARS-CoV-2 coinfection suggested that PLWH do not have an increased risk of COVID-19 and that HIV patients who are compliant to ART and have achieved viral suppression are even less likely to have severe/complicated COVID.[28,30,37,40] From our analysis (Table 1), 228 out of 244 were on ART before being diagnosed with COVID-19. About 76.8% of them were taking nucleoside reverse transcriptase inhibitors (mostly tenofovir and emtricitabine), 89.7% were on integrase strand transfer inhibitors (chiefly, bictegravir and dolutegravir), 77.4% on non-nucleoside reverse transcriptase inhibitors (particularly rilpivirine and efavirenz), while 33.8% were taking protease inhibitors eithers separately or as boosters. Also, 203 out of 378 had viral load suppression (<50 copies per mL) while the data on at least 90% of the remaining were not available. Given these, it is apparent that majority of the patients in these cases were virologically suppressed on ART. This nonetheless did not prevent progression to severe COVID-19 or even death in some patients. A $\chi^2$ analysis of 105 patients whose individual information were available showed that though a great proportion of patient with viral load <50 copies successfully recovered (91.5% vs 81.8% of non-virologically suppressed patients) there is no evidence of association between viral suppression status and severity of COVID-19 ($\chi^2 = 1.068$; $P = .302$) or clinical outcome of patients ($\chi^2 = 1.069$; $P = .301$). Except for only 2 out of 105, all patients where on ART (92 of whom where virologically suppressed),

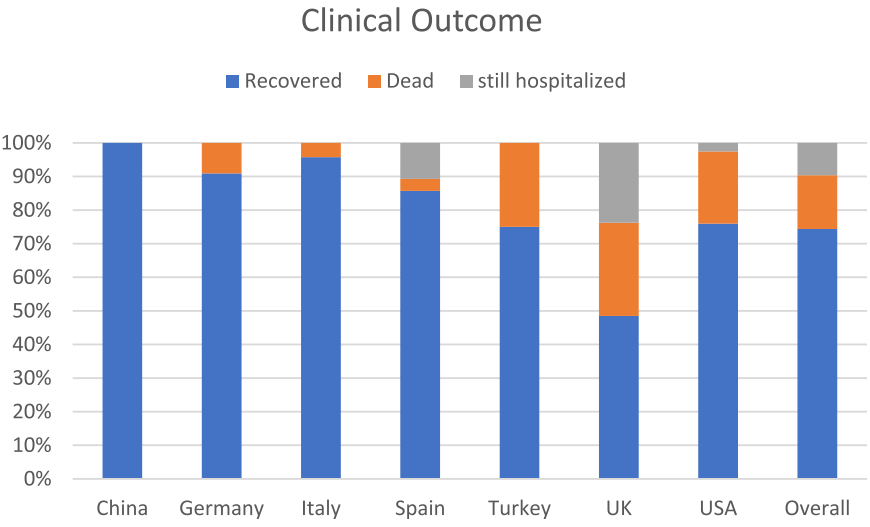


**FIGURE 3** Outcome reported endpoint for HIV/SARS-CoV-2 coinfected patients

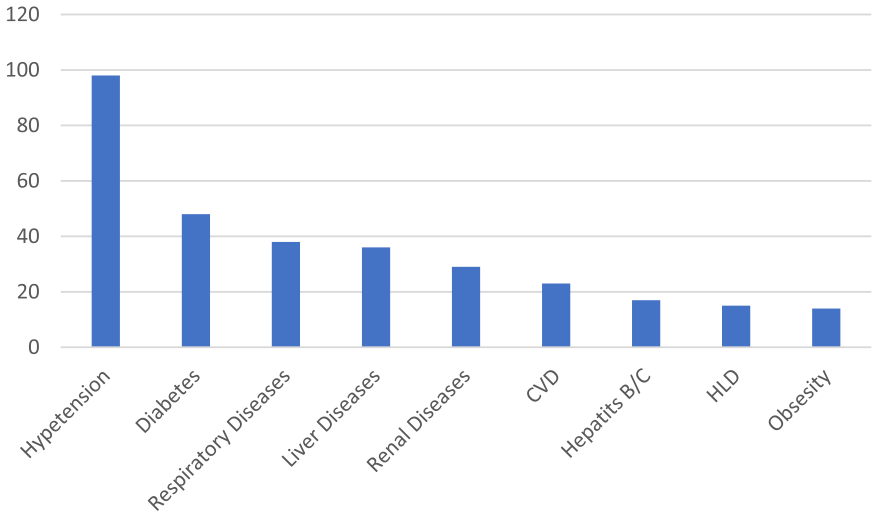


**FIGURE 4** Common comorbidities associated with HIV/SARS-CoV-2 coinfection. CVD, cardiovascular diseases; HLD, hyperlipidemia

yet 22.8% of them had severe/critical COVID-19 while nine died. This therefore raises significant concerns over earlier suggestion that PLWH are somewhat immune to severe cases of COVID-19. Suwanwongse and Shabarek[41] previous expressed similar concern when they reported as high as 78% mortality among HIV/SARS-CoV-2 coinfected patients in their facility. The main reason earlier studies hypothesized that ART could confer protection against COVID-19 in PLWH was that antiviral agents, such as remdesivir, tenofovir, and lopinavir showed antiviral activity against SARS-CoV-2 in vitro studies. Despite several observations that some antiviral agents somewhat improve symptoms of COVID-19,[42] at present standard ART does not seem to shield PLWH from COVID-19. Also, given the profound contribution of the immune system, particularly the massive release of cytokines and chemokines, to the severity of COVID-19, earlier reports proposed that HIV-related immunosuppression could paradoxically protect against severe manifestation of COVID-19.[37,43-45] Out of 182 with individual data on CD4 count, 106 had CD4 count ≥200 cells per μL—59.4% of whom had CD4 > 500 cells per μL. Our analysis show an evidence of strong association between immune suppression status (CD4 count <200 or ≥200 cells per μL) and increased severity of disease (n = 119; $\chi^2 = 7.772$; $P = .005$) but not clinical outcome (n = 109; $\chi^2 = 1.191$; $P = .275$). A binary regression analysis further showed that CD4 count <200 cells per μL increases the risk of progression to severe COVID-19 by almost 5 (odds ratio = 4.92; 95% confidence interval, 1.48-16.37). About 61% of cases with CD4 <200 cells per μL had complicated COVID-19 manifestation of which two died. Thus, contrary to earlier suggestions that coinfection patients may have mortality benefits from HIV-related immunosuppression, low CD4 count below 200 per μL may rather predispose them to severe forms of the disease. Two hundred and sixty-nine of the patients were reported to be hospitalized while 109 were reported to be outpatients. The large number of hospitalized patients is mainly due to the fact that most of the case and series reports considered in this paper were of inpatients. As such we are unable to estimate if coinfection influence the hospitalization rate. Currently several medical comorbidities including hypertension, diabetes, respiratory disease, CVD, kidney disease, liver disease, hepatitis infection, etc. have been identified as risks factors associated with severe disease manifestation and poor prognosis.[26,27,38] Out of 237 cases with information on comorbidities, 151 (63.7%) had at least one comorbidity. Hypertension was the most prevalent comorbidity observed in coinfected patients followed by diabetes (Figure 4). In the original case reports included in this study, a great part of the of the dead were reported to have multiple comorbidities. Thus, it is possible the higher overall case-fatality rate reported earlier (14%) was compounded by these other comorbidities and not sole contribution of HIV infection. Nevertheless, HIV infection is generally characterized by various comorbidities [46] and associated morbidity and mortality are inevitable.

## 4 | CONCLUSION

It is generally accepted that, at present, our knowledge about the coronavirus is not definite and keeps evolving with emerging evidence, nonetheless, the preliminary analysis of available evidence shows that PLWH are not protected from COVID-19 or severity of the disease. Also, HIV-related immunosuppression may increase risk of severity of COVID-19 instead confer protection. While the study does not show excess morbidity and mortality among PLWH, especially those with viral load suppression on ART, people living with HIV ought to be vigilant and adhere strictly to guidelines and recommendations of how to keep themselves safe from SARS-CoV-2 infection.

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### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

ONK and PA contributed to the ideas and organization of the content and wrote the manuscript. All authors have read and approved this final version of the manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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